

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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REC'D 10 SEP 2004

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1.)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/000134

International filing date (day/month/year)
12.01.2004

Priority date (day/month/year)
13.01.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/22, A61K38/17, A61K38/27, A61P43/00

Applicant
RAPPOLD-HOERBRAND, Gudrun

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Merckling-Ruiz, V



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2004/000134**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2004/000134**Box No. II Priority**

1. The following document has not been furnished:

copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
 translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	1-11,13-17
	No: Claims	12
Inventive step (IS)	Yes: Claims	1-11,13-17
	No: Claims	12
Industrial applicability (IA)	Yes: Claims	1-17
	No: Claims	

2. Citations and explanations**see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/000134

1. Reference is made to the following documents :

D1: WO 01/34181 A (RAO ERCOLE ; RAPPOLD HOERBRAND GUDRUN (DE))
17 May 2001 (2001-05-17)

D2: EP-A-1 260 228 (RAPPOLD HOERBRAND GUDRUN) 27 November 2002
(2002-11-27)

D3: RAO E. ET AL.: "The Leri-Weill syndrome homeobox gene SHOX encodes a cell-type specific transcriptional activator." HUMAN MOLECULAR GENETICS, vol. 10, no. 26, 2001, pages 3083-3091, XP002293247

D4: WO 02/074234 A (PROCHON BIOTECH LTD ; YAYON AVNER (IL); GOLEMBO MYRIAM (IL)) 26 September 2002 (2002-09-26)

D5: DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; Abstract No. NLM1070532 2002, BETTENCOURT P.: "Bain natriuretic peptide (nesiritide) in the treatment of heart failure." XP002293248

Unless specified otherwise, the relevant passages are the ones that are cited in the Search Report.

Regarding point V

2. The use of natriuretic peptides ANP or BNP, alone or in combination with other active agents, for the manufacture of a medicament for treating short stature in patients suspected of having a defect in the SHOX gene has not been previously disclosed. Claims 1-11 and 17 are novel.

2.1 Claim 12 is directed to a composition comprising ANP or BNP, the other technical features being non-limiting for the scope of the claim. Such a composition is anticipated in D5.

2.3 There is no prior disclosure of a composition comprising ANP or BNP in combination with growth hormone or SHOX peptide. Claims 13-16 are novel.

**WRITTEN OPINION OF THE
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International application No.

PCT/EP2004/000134

3. The technical problem solved by the application is to provide a therapeutic agent for treating short stature related to a defect in the SHOX gene.

In D2, the same technical problem is solved by administering a SHOX peptide, alone or in combination with growth hormone, to patients having a defect in the SHOX gene. The relationship between expression of SHOX and ANP or BNP is not mentioned.

In D4, the natriuretic peptide CNP is used for stimulating bone elongation in patients with abnormal bone growth. ANP and BNP are mentioned (page 10 lines 18-22) but the whole application is directed to the use of CNP only. D4 is not an enabling disclosure for the use of ANP or BNP as therapeutic agents.

It follows that the subject matter of claims 1-11 and 13-17 is inventive over the prior art.